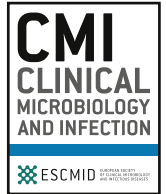




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Letter to the Editor

Reply to the Letter to the Editor—Clinical prediction rules used to rule out endocarditis must be assessed against a sensitive reference standard

Dear Sir,

We are grateful for the thoughtful comments by Heriot et al. [1] and appreciate the opportunity to respond.

We agree that the reference standard of modified Duke criteria should be ideally based on a trans-oesophageal echocardiography (TOE), which is more accurate than a trans-thoracic echocardiography (TTE) [2]. Since a significant proportion of *Staphylococcus aureus* bacteraemia patients in most studies had a TTE without a TOE, there is the potential to miss the diagnosis of infective endocarditis (IE).

In their graph, Heriot et al. [1] demonstrate a potential positive relationship between TOE usage and proportion of IE diagnoses in studies. From a review of the 30 studies described in our systematic review [3], we found nine additional studies that described the TOE rate and IE prevalence based on the Duke criteria or modified Duke criteria (Fig. 1). The additional data points seem to deviate from the original generalized linear model fitted line as proposed by Heriot et al.

There may be other contributing factors to explain this relationship other than more accurate detection of IE on a TOE. First, as Heriot et al. [1] stated that, 'the application of TOE in these series is not random, and is almost certainly related to the clinician's assessment of endocarditis risk.' Patients at high risk for IE were more likely to undergo TOE based on physician's discretion. Hence, the selection for TOE would be a confounder, because patients considered to be high risk for IE were more likely to undergo TOE and were also more likely to have IE that was not related to TOE findings. Second, TOE rates correlate with use of any echocardiography (TTE and/or TOE). Studies that used TOE also used TTE more often, so decreasing the number of cases where no echocardiography was carried out (Fig. 2). Although there is a positive correlation, the rate of TOE cannot account entirely for the increase in the rate of any echocardiography (Fig. 2). The median difference between the rate of any echocardiography and the rate of TOE is 27% (interquartile range 11%–46%) across studies, which is the rate of TTE without TOE. The rate of any echocardiography seems to be related with higher IE prevalence (Fig. 3). Perhaps it is the echocardiography (TTE and/or TOE) rate that increases the detection of IE, where it does not matter whether it is by TTE versus TOE and TOE rate merely reflects the echocardiography rate, nothing more.

The systematic review cited by Heriot et al. [1] shows that consultation with an Infectious Diseases specialist increased rates of echocardiography and increased the rate of IE diagnoses [4]. However, the systematic review does not differentiate between TTE and TOE [4]. It is difficult to extrapolate from these data to Heriot et al.'s point of increased IE diagnosis due specifically to a higher TOE rate.

Heriot et al. [1] describes two potential biases. First bias is incorporation bias, which is the same point that we raised in our paper. In the discussion section, we wrote, 'Another limitation is that some predictors in our study and in existing clinical prediction rules are also present as part of the minor criteria in the reference standard, the modified Duke criteria ... This incorporation bias tends to increase the diagnostic properties for these predictors' [3]. The second bias is selection bias. Although Heriot et al. emphasize the selection bias for TOE, we believe that the selection bias of excluding patients with no echocardiography is more important and takes precedence. In our paper, we wrote, 'In many studies, a significant proportion of (*S. aureus* bacteraemia) patients who did not receive echocardiograms were excluded. This exclusion introduces potential selection bias and makes study results less applicable to all (*S. aureus* bacteraemia) patients' [3]. The same rationale applies to selection of TOE in selected high-risk patients. The potential for missing the diagnosis of IE using no echocardiography compared with any echocardiography (TTE and/or TOE) is far greater than that of TTE compared with TOE. Using the example of Heriot et al., [1] that of the study by Khatib et al., the fact that 498/877 (57%) patients with *S. aureus* bacteraemia did not receive any echocardiography is far more concerning for risk of bias than the fact that 177/877 (20%) patients received a TOE [5].

Nonetheless, Heriot et al. [1] make a valid argument that the ideal reference standard should be the modified Duke criteria based on TOE. This is reiterated in our study. In the Discussion section, we wrote, 'Ideally, as the reference standard, the modified Duke criteria should be based on TOE findings instead of TTE findings, given that TOE is more accurate' [3]. As the reference standard, TOE would need to be applied to all *S. aureus* bacteraemia patients consecutively in a study, which may not be feasible. In a study with a hospital policy of TOE for all *S. aureus* bacteraemia cases, only 60% received TOE [6]. To our knowledge, the highest reported TOE rate approaches only 70% [7]. While waiting for a study that employs universal TOE, our study summarizes the best currently available evidence.

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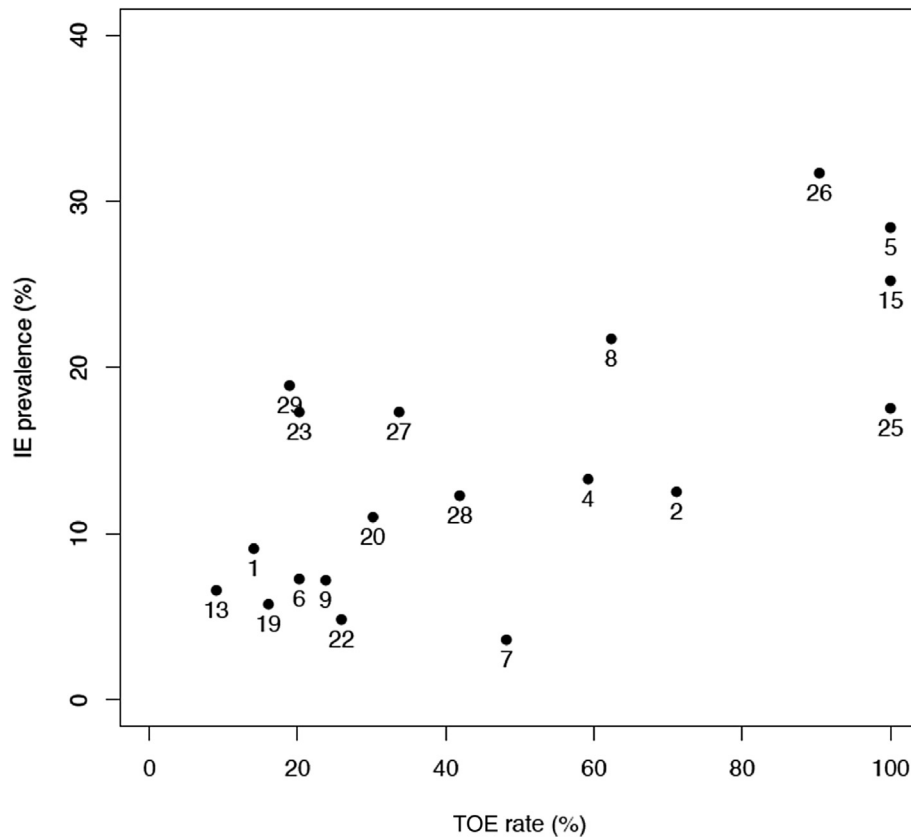


Fig. 1. Relationship between trans-oesophageal echocardiography (TOE) and infective endocarditis (IE). Numbers in graph correspond to the numbered references in Appendix 2 of the original review by Bai et al. Note that reference 6 in the graph (Khatib et al. 2013) uses trans-oesophageal echocardiography, not modified Duke criteria, as the reference standard. It was included, because it was included in the original graph by Heriot et al. [1].

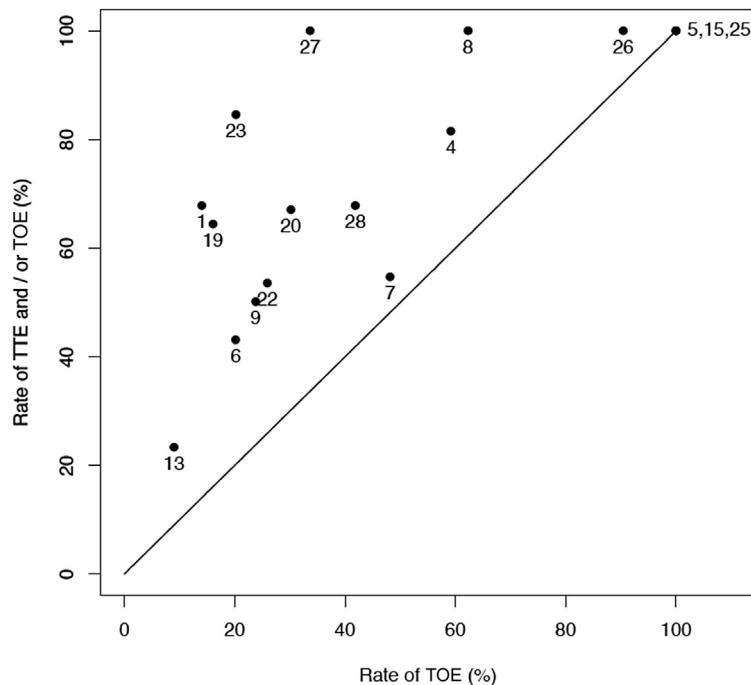


Fig. 2. Relationship between trans-oesophageal echocardiography (TOE) and any echocardiography (trans-thoracic echocardiography (TTE) and/or TOE). The solid line is based on the equation of $y = x$. The vertical distance from the line to each point is the additional percentage of TTE and/or TOE above the TOE rate, which corresponds to the rate of TTE without TOE. Numbers in graph correspond to the numbered references in Appendix 2 of the original review by Bai et al. Note that reference 6 in the graph (Khatib et al. 2013) uses trans-oesophageal echocardiography, not modified Duke criteria, as the reference standard. It was included, because it was included in the original graph by Heriot et al. [1].

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